Declaration of Dr. Jean-Marie Saint-Remy under 37 CFR § 1.132

I, Jean-Maire Saint Rémy declare and state as follows. I am a professor at the University of Leuven and I am an expert in the field of vascular biology. I am one of the inventors of the U.S. Patent Application No. 10/044,569 entitled 'Method and pharmaceutical composition for preventing and/or treating systemic inflammatory response syndrome'.

I understand that the Examiner has questioned, in the Office Action mailed on April 21st, 2004, the fact that monoclonal antibodies against the C1 domain of FVIII of the invention, which are partial inhibitor of FVIII, have a therapeutic application in the prevention and/or treatment of systemic inflammatory response syndrome, as seen e.g. in sepsis.

As indicated in the description of the application under examination, the antibodies developed against the C1 domain of FVIII are of particular interest in the treatment of systemic inflammatory response syndrome, because they are partial inhibitors of FVIII, which allows administration at increased dosages, without the occurrence of side-effects typical of complete FVIII inhibition. The amount administered can thus be upregulated (if necessary for each patient individually) until the desired effect is achieved.

I herewith present additional data from an animal model which confirm that antibodies, directed to the CI domain of FVIII, and partially inhibiting FVIII activity in mice, have a beneficial effect on the prevention of septic shock.

The model that was used, i.e. the induction of sepsis by a single bolus injection of LPS in mice, is a well-established model for studying the symptoms and testing potential therapeutic agents in septic shock.

We prepared in our laboratory monoclonal antibodies against the C1 domain of human factor VIII, that are capable of partially inhibiting FVIII in mice, wich will be referred to as LE2E9Q hereafter.

Wildtype C57Bl/6 mice were injected with LE2E9Q, a sham IgG4 antibody (AK6A3) or buffer. Thirty minutes later a single IP injection of 400 µg LPS was administered. Mice were followed up for survival. It was observed that the LE2E9Q antibodies, can be administered in high dosages without occurrence of shock as a result of pro-inflammatory and anti-inflammatory compensatory responses as observed with complete inhibition of FVIII. The results on prevention of sepsis are illustrated in Figure 1. This Figure shows a highly significant death prevention with 30 µg of LE2E9Q as compared to no antibody (Kaplan-Mayer test, $p < 0.03$), an irrelevant IgG4 antibody ($p < 0.03$).

These results clearly demonstrate that antibodies with a partial inhibitory activity on FVIII in mice can prevent septic shock in the mouse model.

I hereby declare that all statements made herein are true and are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statement may jeopardise the validity of the application or any patent issued thereon.

Date:

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By: Dr. Jean-Marie Saint-Remy

Figure 1.

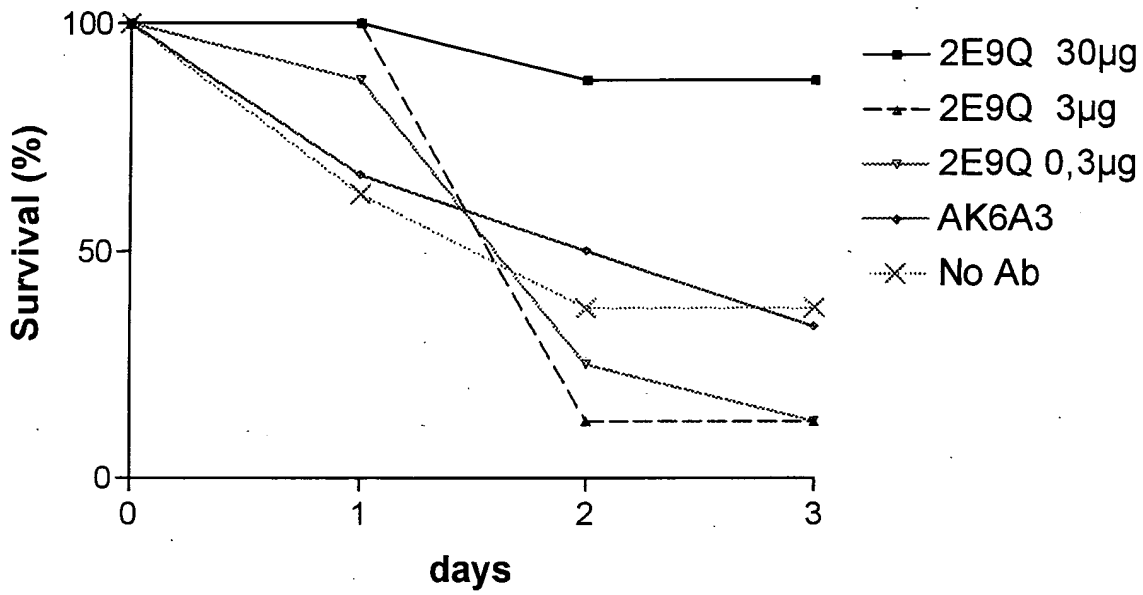

Figure 1: Survival in a septic shock model of mice pretreated with partial inhibitory antibodies against Factor VIII.